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Interventions for the reduction of prescribed opioid use in chronic non-cancer pain (Review)

Windmill J, Fisher E, Eccleston C, Derry S, Stannard C, Knaggs R, Moore RA



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Interventions for the reduction of prescribed opioid use in chronic non-cancer pain

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ABSTRACT

Background

Patients with chronic non-cancer pain who are prescribed and are taking opioids can have a history of long term high dose opioid use without effective pain relief. In those without good pain relief, reduction of prescribed opioid dose may be the desired and shared goal of both patient and clinician. Simple unsupervised reduction of opioid use is clinically challenging, and very difficult to achieve and maintain.

Objectives

To investigate the effectiveness of different methods designed to achieve reduction or cessation of prescribed opioid use for the management of chronic non-cancer pain.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 8th April 2013, as well as bibliographies.

Selection criteria

Included studies had to be randomised controlled trials comparing opioid users receiving an intervention with a control group receiving treatment as usual, active control, or placebo. The aim of the study had to include a treatment goal of dose reduction or cessation of opioid medication.

Data collection and analysis

We sought data relating to prescribed opioid use, adverse events of opioid reduction, pain, and psychological and physical function.

Main results

Two studies provided information on 86 participants. One compared electroacupuncture with sham acupuncture for 20 minutes twice a week for six weeks; there was no difference between treatments. The other followed 11 weeks of cognitive behavioural therapy with either therapeutic interactive voice response through a computer for four months or usual treatment; the active group had a significant reduction in opioid use, while the usual care group had a significant increase.

Authors' conclusions

Both included studies were at significant risk of bias because of their small size, together with other important issues, including blinding. Because of this risk and the paucity of relevant studies, no conclusions can be drawn regarding the effectiveness of interventions for opioid withdrawal in chronic non-cancer pain.

PLAIN LANGUAGE SUMMARY

Reducing prescribed opioid use in chronic non-cancer pain

About 1 in 5 adults suffer from moderate or severe chronic pain that is not caused by cancer. Some people with this type of pain are treated with opioids (typically with drugs like morphine, codeine, oxycodone, fentanyl, or buprenorphine, either as tablets or as patches placed on the skin). It is not unusual for this medication to be ineffective or to stop working over time, and, sometimes, effective pain relief is not achieved despite doses being increased. Stopping using opioid drugs is not easy, especially when they have been used for some time, because stopping abruptly can cause unpleasant side effects. This review looked for high quality studies (randomised controlled trials) of treatments to help people safely stop taking opioids prescribed for their pain. Only two studies were found, and they investigated only 86 people. No conclusions can be drawn from this small amount of information. Non-randomised studies, not included in this review, do indicate that in most people intensive rehabilitation packages can bring about major reduction in opioid use. Reducing prescribed opioid use in chronic non-cancer pain is an important topic in need of more research.

BACKGROUND

Chronic pain of moderate or severe intensity and lasting six months or longer affects around 20% of adults and imposes significant reduction in quality of life (Moore 2013). Opioids have long been used in the treatment of acute and cancer pain, and over the last two decades there has been a marked increase in their prescription for chronic non-cancer pain (CNCPP), especially in the US, Australia, and Europe. Estimates of the numbers of people with chronic non-cancer pain treated with opioids are not commonly available, but one estimate for the UK indicates that almost one million people may use some form of opioid (Gallagher 2009).

Several randomised controlled trials suggested that opioids provide modest pain relief in the short to medium term (typical trial duration is 12 weeks; Kalso 2004; Furlan 2006). However, there is much less evidence that opioids provide long term pain relief in CNCPP (ASIPP 2012; Noble 2010), especially when statistical imputation methods where withdrawal for any reason is regarded as treatment failure (and relevant to clinical practice) are used in favour of carrying the last observed pain readings to the end of the trial and using that measurement to estimate efficacy despite the patient not taking the medicine (not, therefore, relevant to clinical practice) (Moore 2012; Steiner 2011).

Adverse events, principally sedation, impaired cognitive function, depression, constipation, and bladder dysfunction, are also common during opioid therapy (Benyamin 2008), with up to

80% of users suffering at least one adverse event (BPS 2010; Moore 2005). Long-term opioid use can be associated with immune system depression, hormonal disturbances, and hyperalgesia (Benyamin 2008), as well as fractures (Miller 2011), and increased all-cause mortality in older people compared with other analgesics (Solomon 2010). Opioid use also carries risks of tolerance, dependence, and abuse.

Practicalities of the real world like prescribing restrictions for non-opioid analgesics, or guidelines that suggest early use of opioids, can mean that many patients are prescribed opioid drugs, sometimes inappropriately. The American Society of Interventional Pain Physicians suggests that the majority of patients who start chronic opioid treatment continue with the treatment throughout their life (ASIPP 2012). On occasion, opioid doses are increased as a result of insufficient analgesia or the development of tolerance (ie, requiring a higher dose to obtain the same therapeutic benefit). This can lead to patients being prescribed very high doses of opioids, but still without acceptable pain relief. American opioid sales quadrupled between 1999 and 2010 (ASIPP 2012). In the US, increased prescribing is associated with higher rates of overdose and overdose death (Paulozzi 2011), but with an indication that 60% of CNCPP opioid deaths occurred while opioids were used as directed (ASIPP 2012). The link between opioid prescribing and opioid-related death is unclear, but rapid increases in opioid prescribing are being seen in Australia (Leong 2009), and in England there was a 101% increase in the number of prescriptions for

strong opioids between 2004 and 2011 ([NHS Information Centre 2012](#)).

A number of professional societies worldwide have produced guidance advocating/promoting the judicious and careful use of opioids. The American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine jointly advise that health care providers should exercise caution when prescribing opioids, assessing circumstances and suitability on an individual basis ([Chou 2009](#)). Guidance in Washington State ([Washington State Agency Medical Group 2010](#)) has passed into law ([HB2876 2010](#)). Current UK guidance is typical in that it recognises that prescription opioids can lead to problem use, and that there is considerable uncertainty in the literature about any long term benefits of continued use. The British Pain Society guidance on opioids for persistent pain ([BPS 2010](#)) is particularly cautious. Similar cautions have been raised for prescribers in Australia ([McDonough 2012](#)).

There is growing concern that the widespread use of opioids has public health implications ([Stannard 2012](#)). The balance between benefit and risks generated during long term therapy with opioids suggests that it may be neither clinically effective nor in patients' best interests to continue opioid prescription without adequate pain relief. There is, therefore, a potential need to facilitate and maintain opioid dose reduction. For many patients it is likely that long-term opioid treatment is continued even when benefit is not demonstrated, and greater patient benefits may accrue from opioid withdrawal. Patients who do not benefit from treatment in terms of pain, or who suffer unacceptable adverse events, should be helped to cease opioid treatment whilst concurrently addressing their pain ([Ballantyne 2003](#)).

There is a growing recognition that many patients will reach a state where the reduction of prescribed opioids is the desired and shared goal of both patient and clinician. This state is sometimes reached after a history of long term high dose opioid use, making simple unsupervised cessation clinically challenging, if not impossible. This may occur, at least in part, because of the reluctance of patient and prescriber to reduce opioid dose for fear of worsening pain, as well as issues of dependence and subsequent withdrawal symptoms.

There are many studies of methods of withdrawal from opioids; most, however, are undertaken in the context of addiction services for patients with an opioid abuse problem. Our interest here was in the planned reduction or total withdrawal of opioids prescribed for pain management. Common opioid reduction techniques in the addiction field are instructive and include opioid replacement stabilisation and dose tapering and may involve psychological treatments ([Amato 2011](#)). Inducing withdrawal under sedation using opioid antagonists such as naloxone, naltrexone, or nalmefene is possible ([Gowing 2009](#); [Gowing 2010](#)) but is not recommended owing to unacceptable risks of adverse events. It is

unclear whether similar interventions are effective when adjusted to CNCP in which treatment aims differ, or if other approaches are more appropriate.

Description of the condition

Patients

1. with chronic pain of a non-cancer-related origin
2. who are prescribed opioid medication for pain management
3. who have a treatment goal of dose reduction or cessation of opioid medicine

Description of the intervention

The intervention may be any clinical method that aims to facilitate opioid withdrawal or dose reduction as a compulsory or optional aspect of treatment, as either a primary or a secondary outcome. The intervention could be pharmacological, physiological, psychological, or another, as long its methods are documented clearly within the study.

How the intervention might work

Different methods will have different mechanisms. In particular, we expect non-pharmacological treatment aimed at opioid reduction to operate principally through behaviour change, and pharmacological methods to operate principally by reducing or managing the adverse events of opioid use or opioid withdrawal.

Why it is important to do this review

Increased prescribing of opioids is a problem because of their potential to cause harm, along with issues of limited relief and tolerance. Given the known risks of opioid therapy, it is appropriate to continue to prescribe opioid medicines only to those patients for whom the treatment produces acceptable benefits, weighed against any adverse events. Given evidence in many societies of huge increases in the use of medicinal opioids for CNCP, their limited effectiveness, and their adverse event profile, we can reasonably expect a large increase in patients seeking clinical help to reduce or halt opioid consumption. An evidence summary of the most effective methods is needed, along with guidance on treatment development.

OBJECTIVES

To investigate the effectiveness of different methods designed to achieve reduction or cessation of prescribed opioid use for the management of CNCP.

METHODS

Criteria for considering studies for this review

Types of studies

Included studies had to be randomised control trials (RCTs) comparing opioid users receiving an intervention with a control group receiving treatment as usual, active control, or placebo. The aim of the study had to include a treatment goal of dose reduction or cessation of opioid medicine.

Types of participants

Participants were adults (18 years of age or older) using prescription opioids for management of chronic non-cancer pain with a duration of at least three months. Pain conditions could include but were not limited to: neuropathic pain, myofascial pain, back pain, fibromyalgia, headache, abdominal, neck or musculoskeletal pain.

We excluded studies involving only participants with issues of addiction, abuse, dependence, or non-prescribed opioid use, and involving participants using opioids for pain relief during palliative care. This is because the aims of treatment for these populations differ substantially from those for the population of interest.

Types of interventions

We planned to include in this review a large variety of intervention types. Interventions could be based in pharmacology, physiology, psychology, spirituality, or another approach, provided that the underpinning methodology was well documented in the study and was valid. Eligible intervention types could include opioid antagonist treatment, dose tapering, or opioid replacement with other pain relieving medication. Interventions could also involve physical therapy, massage, disability management, complementary therapies, or psychological approaches such as cognitive behavioural therapy, counselling, and coping techniques.

We excluded studies encompassing only interventions specifically for opioid addiction, medication overuse, dependence, or withdrawal symptoms.

Types of outcome measures

We extracted relevant outcomes before treatment, immediately after treatment, and at follow-up, at least three months later but no longer than a year. If there were two follow-up time points, the later would be chosen.

Primary outcomes

The primary outcomes of this review are prescribed opioid use in adults, and the adverse events related to opioid reduction.

Secondary outcomes

Secondary outcomes are symptom reporting of pain, psychological functioning, and physical functioning.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE from inception to 8th April 2013, for RCTs meeting inclusion criteria, with no restrictions placed on language. See [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#) for the MEDLINE (via Ovid), EMBASE (via Ovid), and CENTRAL search strategies.

Searching other resources

We searched the reference lists of retrieved papers and carried out a citation search to identify any potentially eligible papers not found through the electronic search. We also contacted the authors of studies identified for inclusion to obtain additional data relevant to this review and not included in the published articles.

Data collection and analysis

Selection of studies

We filtered search results initially by title and abstract, and obtained full copies of potentially eligible studies. Two review authors read the studies to confirm eligibility, with disagreements discussed and mediated by a third review author if necessary. After the search was conducted, we limited the selection of studies to those published from 2000 onwards, to reflect the major growth in recent years in opioid prescribing for chronic non-cancer pain.

Data extraction and management

Two review authors extracted data using a standard data extraction form to include details of participants, intervention method and duration, quantity and type of opioid used, study design, and treatment outcomes. We discussed any discrepancies with a third review author.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies using the Cochrane Collaboration Risk of bias tool to assign judgements of high, low, or unclear risk of bias to sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and any other potential sources of bias in the included studies.

Measures of treatment effect

We planned to use risk ratio (RR) to establish statistical difference, and number needed to treat for an additional beneficial outcome (NNT) and number needed to treat for an additional harmful outcome (NNH) as absolute measures of benefit or harm.

We defined a 'responder' to treatment as a participant who experienced at least a 50% reduction in opioid consumption, or achieved complete opioid withdrawal or a reduction of their intake to below 'high' dose, which we identified as 120 mg/day oral morphine equivalent. Trials have previously shown that dose-related harms of taking more than 120 mg/day of opioid drugs outweigh the benefits (Braden 2010; Morasco 2010; Sullivan 2010), and published guidelines, including those of the American Pain Society and the American Academy of Pain Medicine (Chou 2009), and by the Washington State Agency Medical Group 2010, recommend a cut-off at 120 mg/day. A responder also had to have, at worst, no increase in pain as a result of the intervention. Both aspects of improvement had to be maintained for at least three months post intervention.

Unit of analysis issues

The unit of analysis was the individual patient.

Dealing with missing data

We used the intention-to-treat approach to deal with missing data. We would include in the analysis all participants who were randomised to treatment, and those for whom follow-up data were not available were assumed to be non-responders.

Assessment of heterogeneity

It was anticipated that there would be significant clinical heterogeneity between studies (participants, conditions, interventions), so we planned to pool data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to assess the effect of entry dose on intervention efficacy, and to compare outcomes between pain conditions or intervention type if sufficient data were available.

Sensitivity analysis

We planned to perform a sensitivity analysis should we suspect that studies with high risk of bias were significantly skewing results of a comparison, removing studies from the analysis to assess their influence.

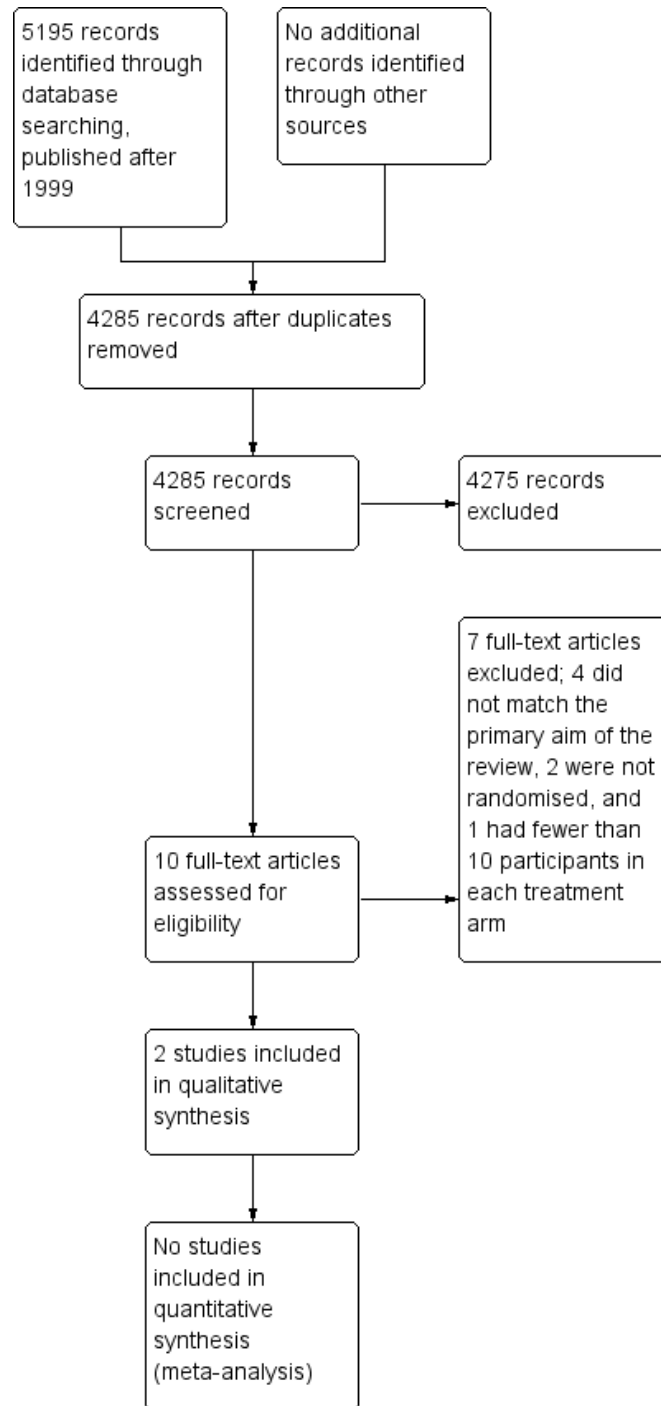
RESULTS

Description of studies

Results of the search

We found 5195 reports in the original search; we identified 4285 reports after duplicates were removed. We identified ten potentially relevant reports from the titles and abstracts, and of these, three met the inclusion criteria of the review (Figure 1).

Figure 1. Study flow diagram.



Included studies

Two studies (three reports) were included in the analysis (Zheng 2008; Naylor 2010), with a total of 90 participants randomised to treatment, and 86 treated. One study (Naylor 2010) reported additional useful information in an earlier publication (Naylor 2008). Full details can be found in the [Characteristics of included studies](#) table.

In addition to published data, the authors of the two included studies provided additional data for the outcomes of pain and psychological functioning ([Appendix 4](#)).

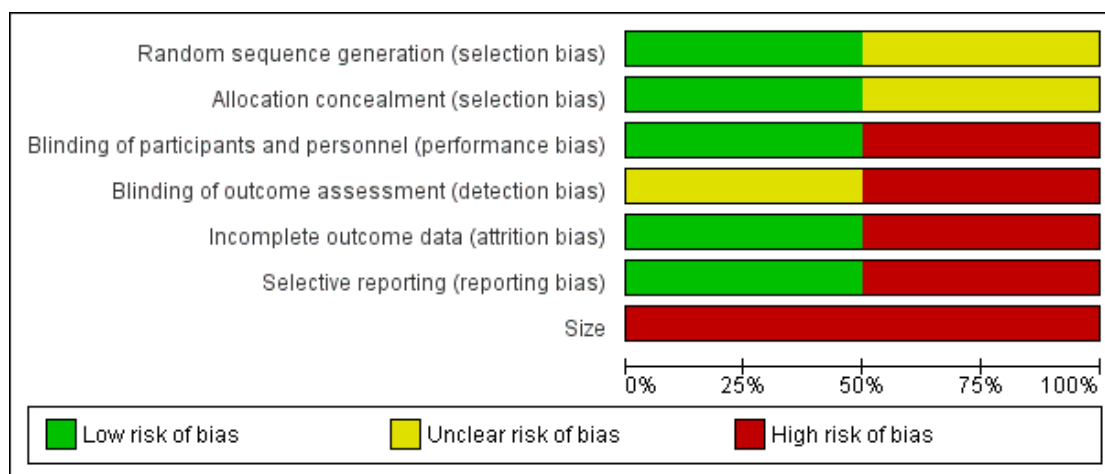
Excluded studies

Seven studies were excluded from analysis. Three did not meet methodological standards (Crisostomo 2008; Krymchantowski 2003; Townsend 2008), while four did not have opioid reduction as a primary aim (Hale 2007; Potter 2010; Roland 2011; Weinstein 2006). Full details are available in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

Both of the studies were at significant risk of bias because of their small size, plus a number of other issues, including blinding ([Figure 2](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

The two included studies used different interventions, and so results were not pooled.

Primary Outcomes

Opioid use

Zheng 2008 randomised participants to receive either real electroacupuncture (REA; $n = 17$) or sham electroacupuncture (SEA; $n = 18$) for 20 minutes twice a week for six weeks. Opioid consumption varied considerably within each group, and the mean consumption at baseline differed between groups, being 462 (\pm

463) mg/week in the REA group and 296 (\pm 288) mg/week in the SEA group. Participants in both groups who completed the six weeks of treatment (REA = 12; SEA = 14) reported a significant reduction in opioid consumption between baseline and the end of treatment at eight weeks, of 64% and 46% in the REA and SEA groups, respectively. In an intention-to-treat analysis, the reductions were 39% and 26%. The difference between groups was not statistically significant. At follow-up at 20 weeks (REA = 9; SEA = 14), opioid consumption had gradually increased in the REA group and was significantly higher at 20 weeks than at eight weeks, while in the SEA group there was no significant change.

Naylor 2010 compared therapeutic interactive voice response

through a computer for four months with usual treatment, following cognitive behavioural therapy for 11 weeks. The experimental group (n = 26, 14 of whom were using opioids at baseline) reported a significant decrease in opioid use from baseline at both four- and eight-month follow-ups, with three participants stopping opioid use entirely. The control group (n = 25, 15 of whom were using opioids at baseline) significantly increased opioid consumption from baseline to the eight-month follow-up, and three more participants began opioid treatment. At eight-month follow-up, the difference in mean opioid dose was significant, with the experimental group using less than the control group.

Adverse events

Zheng 2008 reported a total of 33 adverse events during the treatment period with REA, and 19 with SEA, none of which were serious. Opioid-based adverse events decreased from baseline to eight weeks after treatment by 40% in the REA group and 45% in the SEA group.

Naylor 2010 did not report on adverse events, but contact with the authors confirmed that there were no adverse events associated with treatment.

Secondary Outcomes

Pain

These numbers are from data supplied by the authors (Appendix 4) and differ very slightly from the published data.

Zheng 2008 used the Visual Analogue Scale to assess pain intensity. Average pain at baseline was 4.9/10 in the experimental group and 5.6/10 in the control group, and post-treatment scores were 4.2 and 5.4, respectively. No differences were detected between groups. At 20 weeks average pain scores were 3.6 and 4.6.

Naylor 2010 analysed pain using the McGill Pain Questionnaire, reported in Naylor 2008 (Naylor 2010). The experimental group reported a decrease in typical pain from baseline to eight months from 5.7/10 to 3.4/10, and the control group from 6.8 to 5.7. The difference between groups was statistically significant.

Physical function

Zheng 2008 did not measure physical function.

Naylor 2010 reported physical function using the SF-36 Physical Function composite scale. The experimental group showed a small increase (from 31/100 to 40/100) in functioning over eight months, while the control group did not (29/100 to 31/100). The difference between groups was statistically significant.

Psychological function

Both studies utilised the Beck Depression Inventory as a measure of psychological functioning. The data are those provided by the authors.

Zheng 2008 reported a significant decrease in depression scores from baseline to post-treatment at 8 weeks in the REA group, from 18 to 17. Scores in the SEA group also decreased, from 19 to 15. At final measurement at 20 weeks, the real electro-acupuncture group mean score was 14, and the sham electro-acupuncture group mean score was 15. There was no significant difference between the groups.

Naylor 2010 reported a decrease in scores of depression across the study. The experimental group reported a mean of 17 at baseline, and 8.1 at 8 month follow-up. The maximum score fell from 29 to 22 in the same period. The control group scored an average of 19 at baseline, with a maximum of 51, decreasing to an average of 15, maximum 37, at 8 month follow-up.

DISCUSSION

Summary of main results

There were no adequate data from which to draw any conclusions from two small studies with different interventions and only 86 treated participants.

Overall completeness and applicability of evidence

Because of the very small number of included studies, it was decided to additionally investigate methods of prescription opioid reduction that were not randomised control trials, in case this was a more commonly used study design. We looked at papers from the existing search results and additional reference searching. Inclusion criteria remained the same as in the main search, excepting the criteria of randomised control design.

In contrast to the randomised evidence, there was a much larger body of evidence from observational studies. A three-week, outpatient, intensive, multidisciplinary pain rehabilitation program conducted at the Mayo Clinic Pain Rehabilitation Center demonstrated large reductions in medication use, particularly in use of opioids, in a number of publications in recent years. The three-week programme included stretching, goal setting, stress management, physical therapy, pain management, relaxation, and occupational therapy (Mayo 2013).

Typical opioid use in patients at admission was high, often above 40% and as high as 100%, and at discharge and follow-up was

low, often below 10%. The analyses were retrospective or longitudinal, and not randomised, but represented an interesting body of additional data.

Results like these were obtained for 159 patients with fibromyalgia (Hooten 2007), for 383 patients after fusion or non-fusion spinal surgery, or no surgery (Crisostomo 2008), in a group of 411 patients with a wide range of age and non-cancer pain conditions (Darchuk 2010), and for 634 chronic pain patients of different smoking status (Hooten 2009). In a group of 213 patients all taking opioids on admission, the rate of opioid use at discharge was 7% and remained low for as long as six months after admission (Townsend 2008).

Change in medication use, including opioid medication use, is a common feature of multimodal and multicomponent programmes of cognitive behavioural therapy for chronic pain. The evidence for such programmes in improving disability status and reducing the impact of mental health outcomes is promising (Williams 2012). At present, however, it is not possible to extract and describe the components of such programmes for their effectiveness on medication consumption outcomes, although individual trials report positive effects. A challenge will be to determine methods of analysis, if possible, of such treatment packages with multiple components addressing multiple outcomes.

Others have sought evidence from literature reviews to prevent opioid over-use, and have put forward what is claimed to be an evidence-based algorithmic approach (Atluri 2012).

Legislation (HB2876 2010) has had a major effect on opioid prescribing in Washington State, where a de-facto limit of 120 mg oral morphine equivalent a day is suggested, with higher doses available after consultation with a specialist. An interim assessment showed that about half of physicians followed guidance on opioid prescribing, and that about 90% of them found it useful (DLI 2009). A more recent survey has shown large falls in opioid prescribing (27%), and in the proportion taking more than 120 mg a day oral morphine equivalents (35%), as well as in opioid-related deaths (50%) (Franklin 2012).

Quality of the evidence

The randomised trial evidence was generally of low quality.

Potential biases in the review process

We were not aware of any biases in the review process, although there was a potential for bias in searching for studies. While the intention to reduce opioid use may have been clear, possible interventions may have been disparate.

Agreements and disagreements with other studies or reviews

We found no other similar reviews.

AUTHORS' CONCLUSIONS

Implications for practice

There were too few data in this review to permit any comments about implications for practice.

Implications for research

It is clear that more research is needed, but there was little guidance from the randomised studies included in this review to inform decisions about the design of future randomised trials, or what interventions they might investigate. Indeed it is a moot point whether testing individual interventions is appropriate, given that extant evidence from non-randomised studies indicates that a multifaceted multidisciplinary approach may be preferable.

The Mayo Clinic Pain Rehabilitation Center evidence indicated that a relatively short multifactorial rehabilitation programme might be a reasonable place to begin research, as that single centre appeared to obtain consistently good results. It is possible that the intensity of delivery of the multifactorial programme is as or more important than the details of specific components. In which case, the research agenda becomes one of replication in the first instance, followed by assessment and evaluation. Delivery of an intensive rehabilitation programme would probably have to be refined for particular locations and cultures.

ACKNOWLEDGEMENTS

We acknowledge the help of Jane Hayes and Jo Abbott in developing the search strategy, and the authors of the included studies in providing additional data.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Naylor 2010

Methods	11 weeks plus 120 days duration, randomised, standard care, controlled trial. Assessments at baseline, post intervention, 4 months, and 8 months post intervention
Participants	Diagnosis: chronic musculoskeletal pain 55 participants randomised, 51 participants received allocated intervention Female 44, Male 7 Mean age 46 (SD ± 11.5) years
Interventions	Prerandomisation cognitive behavioural therapy (all participants, n = 55) Therapeutic Interactive Voice Response (n = 26) Standard care (n = 25)
Outcomes	Prescribed medication use: dose and frequency of opioid analgesics, non-steroidal anti-inflammatory drugs, benzodiazepines, and antidepressants Pain: Short Form McGill Pain Questionnaire (MPQ), Pain Symptoms sub scale from the Treatment Outcomes in Pain Survey (TOPS) Psychological function: Beck Depression Inventory (BDI), SF-36 Mental Function Scale, Coping Strategies Questionnaire (CSQ) Physical function: SF-36 Physical Function Scale, TOPS Total Pain Experience Scale
Notes	4 participants were excluded following randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	'randomized using a stratified block design'
Allocation concealment (selection bias)	Low risk	'consecutively numbered, sealed envelopes were prepared for each gender group by the statistician'
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition

Naylor 2010 (Continued)

Selective reporting (reporting bias)	Low risk	Comprehensive reporting of outcomes
Size	High risk	25/26 per group

Zheng 2008

Methods	20 weeks, randomised, single blind, sham controlled trial Assessments at baseline and at 5th, 8th, 12th, 16th, and 20th weeks
Participants	35 participants with non-malignant pain for longer than 3 months, using opioid medication Male 18, Female 17 Mean age 50 years
Interventions	Electroacupuncture (n = 17) or sham electroacupuncture (n = 18) for 20 minutes twice per week for 6 weeks
Outcomes	Prescribed opioid use: dosage of opioid-like medications and adverse events (type and frequency) Pain: pain intensity: visual analogue scale; McGill Pain Questionnaire (MPQ) Psychological function: Beck Depression Inventory (BDI) Physical function: none SF-36 v2 Health Survey
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'block randomisation code was computer generated and stored in a password protected computer'
Allocation concealment (selection bias)	Unclear risk	'considerable efforts were made to ensure.. .the successful blinding of participants and researchers' Comment: method of concealment not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	'A researcher, who was blinded to the treatment allocation, phoned each participant to inform them of the schedule' Participant blinding success was assessed using Perception of EA Treatment Questionnaire, with no significant differences between groups reported

Zheng 2008 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Single blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition is not described adequately
Selective reporting (reporting bias)	High risk	Last observation carried forward used for 9/35
Size	High risk	17/18 per treatment arm

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Crisostomo 2008	Not randomised
Hale 2007	Primary aim of study was not in line with this review
Krymchantowski 2003	< 10 participants in each arm at post-treatment
Potter 2010	Primary aim of study was not in line with this review
Roland 2011	Primary aim of study was not in line with this review
Townsend 2008	Not randomised
Weinstein 2006	Primary aim of study was not in line with this review

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. MEDLINE search strategy (via Ovid)

1. exp Pain, Intractable/ or exp Chronic Pain/
2. Fibromyalgia/
3. exp Headache Disorders/
4. exp Arthritis/
5. (pain* or headache* or migraine* or neuralgia* or neuropath* or arthriti* or osteoarthritis*).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Analgesics, Opioid/
8. (morphine or meperidine or methadone or buprenorphine or fentanyl or hydrocodone or oxycodone or codeine).mp.
9. (opioid* or opiate* or papaver).mp.
10. exp Narcotics/
11. 7 or 8 or 9 or 10
12. exp Rehabilitation/
13. rehabilitation.fs.
14. Opiate Substitution Treatment/
15. exp Narcotic Antagonists/
16. (diprenorphine or nalmeferine or nalorphine or naloxone or naltrexone or methadone or buprenorphine or clonidine or lofexidine or guanfacine).mp.
17. exp Psychotherapy/
18. psychotherap*.mp.
19. ((cogniti* or behaviour* or behavior* or family or psychosocial*) adj5 (therap* or intervention*)).mp.
20. (counsel* or cope or coping).mp.
21. exp Physical Therapy Modalities/
22. exp Mind-Body Therapies/
23. (physical* adj5 therap*).mp.
24. physiotherap*).mp.
25. (biofeedback* or massage* or acupuncture).mp.
26. pastoral care/ or spirituality/
27. Adaptation, Psychological/
28. (well being or well-being or relax* or accept* or meditat* or spiritual*).mp.
29. (withdraw* or wean* or detox* or cease or cessation or reduc* or taper* or stop* or terminat* or remove* or substitu*).mp.
30. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. 6 and 11 and 30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomized.ab.
35. placebo.ab.
36. clinical trials as topic.sh.
37. randomly.ab.
38. trial.ti.
39. 32 or 33 or 34 or 35 or 36 or 37 or 38
40. 31 and 39

41. exp animals/ not humans.sh.
42. 40 not 41
43. (post-operative or postoperative).mp.
44. 42 not 43
45. limit 44 to ("young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")

Appendix 2. EMBASE search strategy (via Ovid)

1. exp chronic pain/ or exp intractable pain/
2. exp arthritis/
3. (pain* or headache* or migraine* or neuralgia* or neuropath* or arthriti* or osteoarthritis*).ti,ab.
4. 1 or 2 or 3
5. exp narcotic analgesic agent/
6. exp narcotic agent/
7. (morphine or meperidine or methadone or buprenorphine or fentanyl or hydrocodone or oxycodone or codeine).ti,ab.
8. (opioid* or opiate* or papaver).ti,ab.
9. 5 or 6 or 7 or 8
10. exp rehabilitation/
11. rh.fs.
12. opiate substitution treatment/
13. exp narcotic antagonist/
14. (diprenorphine or nalmefene or nalorphine or naloxone or naltrexone or methadone or buprenorphine or clonidine or lofexidine or guanfacine).ti,ab.
15. exp psychotherapy/
16. ((cogniti* or behaviour* or behavior* or family or psychosocial*) adj3 (therap* or intervention*)).ti,ab.
17. exp physiotherapy/
18. exp alternative medicine/
19. ((physical* adj3 therap*) or physiotherap*).ti,ab.
20. (biofeedback* or massage* or acupuncture*).ti,ab.
21. exp counseling/
22. (counsel* or cope or coping).ti,ab.
23. exp religion/
24. adaptive behavior/
25. (well being or well-being or relax* or accept* or meditat* or spiritual*).ti,ab.
26. (withdraw* or wean* or detox* or cease or cessation or reduc* or taper* or stop* or terminat* or remove* or substitu*).ti,ab.
27. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. 4 and 9 and 27
29. crossover procedure/
30. double-blind procedure/
31. randomized controlled trial/
32. single-blind procedure/
33. random*.mp.
34. factorial*.mp.
35. (crossover* or cross over* or cross-over*).mp.
36. placebo*.mp.
37. (double* adj blind*).mp.
38. (singl* adj blind*).mp.
39. assign*.mp.
40. allocat*.mp.
41. volunteer*.mp.
42. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41

Appendix 3. CENTRAL search strategy

1. MeSH descriptor Pain explode all trees
2. (MeSH descriptor Fibromyalgia, this term only)
3. (MeSH descriptor Headache Disorders explode all trees)
4. (MeSH descriptor Arthritis explode all trees)
5. (pain* or headache* or migraine* or neuralgia* or neuropath* or arthriti* or osteoarthritis*)
6. (#1 OR #2 OR #3 OR #4 OR #5)
7. (MeSH descriptor Analgesics, Opioid explode all trees)
8. (morphine or meperidine or methadone or buprenorphine or fentanyl or hydrocodone or oxycodone or codeine)
9. (opioid* or opiate* or papaver)
10. (MeSH descriptor Narcotics explode all trees)
11. (#7 OR #8 OR #9 OR #10)
12. (MeSH descriptor Rehabilitation explode all trees)
13. Any MeSH descriptor with qualifier: RH
14. (MeSH descriptor Opiate Substitution Treatment explode all trees)
15. (MeSH descriptor Narcotic Antagonists explode all trees)
16. (diprenorphine or nalmefene or nalorphine or naloxone or naltrexone or methadone or buprenorphine or clonidine or lofexidine or guanfacene)
17. (MeSH descriptor Psychotherapy explode all trees)
18. (psychotherap*)
19. ((cogniti* or behaviour* or behavior* or family or psychosocial*) near/5 (therap* or intervention*))
20. counsel* or cope or coping
21. MeSH descriptor Physical Therapy Modalities explode all trees
22. MeSH descriptor Mind-Body Therapies explode all trees
23. physical* near/5 therap*
24. physiotherap*
25. biofeedback* or massage* or acupuncture*
26. (MeSH descriptor Pastoral Care, this term only)
27. (MeSH descriptor Spirituality, this term only)
28. (MeSH descriptor Adaptation, Psychological, this term only)
29. (well being or well-being or relax* or accept* or meditat* or spiritual*)
30. withdraw* or wean* or detox* or cease or cessation or reduc* or taper* or stop* or terminat* or remove* or substitut*
31. (12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30)
32. (#6 AND #11 AND #31), from 2002 to 2012
33. MeSH descriptor Pain, Postoperative explode all trees
34. (#32 AND NOT #33), from 2002 to 2012

Appendix 4. Additional data supplied by authors

Naylor 2010	Baseline	Post intervention	4 months	8 months
McGill Typical Pain				
TIVR	5.7 ± 1.9	5.5 ± 1.7	4.1 ± 2.2	3.4 ± 2.4
Control	6.8 ± 1.5	5.6 ± 1.6	5.7 ± 1.4	5.7 ± 1.7
BDI				
TIVR	16.7 ± 6.5	10.4 ± 6.4	8.1 ± 5.7	8.1 ± 4.8
Control	18.6 ± 11.2	16.7 ± 11.2	16.3 ± 8.3	14.9 ± 8.7

Zeng 2008	Baseline	Treatment		Post treatment			
	Weeks 1, 2	Week 5	Week 8	Week 9	Week 12	Week 16	Week 20
Average pain							
REA	4.9 ± 1.7	4.1 ± 2.3	4.2 ± 2.3	3.9 ± 1.9	4.0 ± 1.8	3.8 ± 1.7	3.6 ± 1.7
SEA	5.6 ± 1.7	5.1 ± 1.7	5.4 ± 2.4	5.1 ± 2.0	5.3 ± 2.2	5.0 ± 2.0	4.6 ± 2.1
BDI total							
REA	18.4 ± 7.1	15.7 ± 9.7	17.1 ± 8.3	Not measured	13.8 ± 8.1	14.1 ± 9.3	14.0 ± 7.5
SEA	19.0 ± 8.3	16.3 ± 10.9	15.3 ± 9.6	Not measured	14.5 ± 10.8	15.2 ± 12.0	14.7 ± 13.2

CONTRIBUTIONS OF AUTHORS

Draft the protocol	JW/EF/CE
Develop a search strategy	JW
Search for studies (usually 2 authors)	JW/EF
Obtain copies of studies	JW
Select which studies to include (2 + 1 arbiter)	JW/AM/SD
Extract data from studies (2 authors)	JW/SD

(Continued)

Enter data into RevMan	JW/AM/SD
Carry out the analysis	JW/AM/SD/CE
Interpret the analysis	JW/AM/SD/CE/CS/RK
Draft the final write-up of the review	JW/AM/SD/CE
Update the review	CE
Content expert name	CE/AM/SD/CR/RK
Author responsible for grammar and language	ALL
Methodologist name	CE
Statistician name	Gavin Stewart

DECLARATIONS OF INTEREST

JW, EF, CE, and CS have no relevant interests to declare.

SD has received research support from charities and from government and industry sources at various times, but none are related to this review.

RAM has consulted for various pharmaceutical companies and has received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions, including (in the past five years) AstraZeneca, Eli Lilly, Flynn Pharma, Furtura Medical, Grünenthal, GSK, Horizon Pharma, Lundbeck, Menarini, MSD, Pfizer, Reckitt Benschkiser, Sanofi Aventis, Uργο, and Vifor Pharma.

RK has no conflict of interest in relation to the work under consideration for publication or relevant financial activities outside the submitted work, although he has attended advisory board meetings and has received honoraria or support to attend scientific meetings from several pharmaceutical companies, some of whom market opioids. RK is Chair, United Kingdom Clinical Pharmacy Association Pain Management Group; Chair, PAIN (Pharmacist Analgesia Interest Network); Member of IASP and several SIGs; Member of IASP task force on pharmacy undergraduate education; and Member of British Pain Society and several SIGs. RK has attended advisory board meetings, has received honoraria or support to attend scientific meetings, or has held research grants for Grünenthal, Reckitt Benschkiser, Napp Pharmaceuticals, Pfizer, Astra Zeneca, and Astellas, some of which market opioids.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We contacted the authors of studies identified for inclusion to obtain additional data relevant to this review and not included in the published articles. The original search for studies was intended to be completed without a time limit, but we limited inclusion to studies published in 2000 and later to reflect major changes since 2000 in prescribing of opioids to large numbers of people with chronic non-cancer pain; in this way, we worked to ensure that the review would have contemporary relevance.